CASE: **LA0112 NP**

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Burton Rodney
Type or print name

Signature

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
TIMUR GUNGOR, ET AL.
APPLICATION NO: **10/775,742**
FILED: **02/10/2004**
FOR: **NOVEL THIAZOLIDINE COMPOUNDS AS CALCIUM SENSING RECEPTOR MODULATORS**

ART UNIT: **1626**
EXAMINER: **STOCKTON, LAURA LYNNE**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF HAO ZHANG

To the Commissioner for Patents and Trademarks:

HAO ZHANG DECLARES AS FOLLOWS:

1. He has a Master's degree and is a chemist specializing in preparation of organic compounds.

2. He was employed in the above capacity at Bristol-Myers Squibb Company for more than 9 years.

3. He is familiar with the laboratory experiments carried out by Ying Chen concerning preparation of chemical compounds.

4. He signed as a witness laboratory notebook entries made by Ying Chen in Notebook No. 48255, pages 101, 102, 103, 104, 105 and 108 (ATTACHMENT C, cover page, and ATTACHMENTS D, E, F, G, H and I', respectively).

5. All of the above notebook pages were signed by Ying Chen prior to October 22, 2001.

6. All of the above notebook pages were witnessed by him prior to October 22, 2001.

7. He is not an inventor of the subject matter claimed in U.S. Application Serial No. 10/775,742.

8. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of application Serial No. 10/755,742 or any patent issued thereon.

Date: 9/25/06

HAO ZHANG

PROPERTY OF

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

BRISTOL-MYERS SQUIBB

NOTEBOOK No. 48255

Ying Chen
AMGEN

Assigned to Ying Chen

Subject _____

Department Name _____

Department Number _____

Date Assigned _____

Date Completed _____

Pages Completed from _____ to _____

Continued from Notebook Number _____

Continued in Notebook Number _____

This notebook cannot be transferred to another person

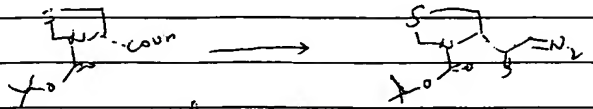
ATTACHMENT C

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

No. 48255-101

DATE: ____ PROJ. NO. 8807 EXPT. NO. ____

SUBJECT ____



Boc-D-thiazolidine-4-carboxylic acid	5.0 g	21.4 mmol
Isobutylchloroformate	2.76 ml	21.4 mmol
Et_3N	30 ml	21.4 mmol
THF	50 ml	
MNNG	11.7 g	
KOH/H_2O	15 g in 37 ml	
Et_2O	125 ml	

To a two phase solution of KOH and Et_2O at 0°C was added MNNG portionly. The ether layer was decanted to a flask. The fresh made CH_2N_2 in Et_2O was kept at 0°C.
To a solution of Boc-D-thiazolidine-4-carboxylic acid, Et_3N in THF at -10°C (acetone + ice) was added dropwise isobutylchloroformate. The reaction was kept at -10°C for 30 min then filtered (white solid was resulted from $Et_3N \cdot HCl$). The filtrate was stirred at -10°C. A solution of CH_2N_2 in Et_2O was added. Stirring was continued for 1h. Then warmed to RT. Et_2O was added and the solution washed with H_2O, Sat'd NaHCO3 brine and dried over MgSO4. Evaporation gave a yellow oil. Purification was performed by flash column on silica gel, loaded with CH_2Cl_2, eluted with 25% EtOAc in Hexane. Pure fractions were combined and evaporated to give a pale yellow oil.

48255-101-27 4.44 g (80.7%)

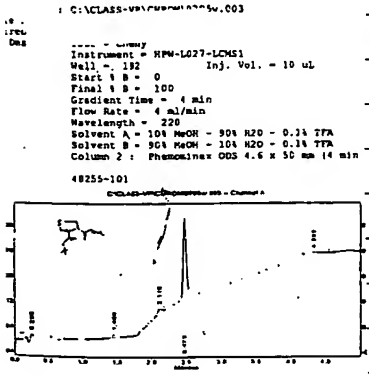
^{1}HNMR

^{13}CNMR (CDCl3, 400 MHz) was consistent

LC-MS M+23 = 280

RQ22912 for MS M+1 = 258

OR



	RT	Area	Area %	Plates
1	0.26	31325	3.367	161
2	3.17	29405	2.946	2134
3	3.32	55962	6.006	7375
4	3.47	455927	49.001	13173
5	4.33	359915	38.682	0

SIGNED ____ DATE ____ WITNESSED AND UNDERSTOOD BY ____ DATE ____

CROSS REFERENCES:

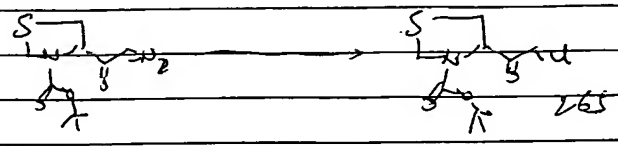
ATTACHMENT D

DO NOT WRITE IN THIS MARGIN

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

DATE: _____ PROJ. NO. 08001 EXPT. NO. _____

SUBJECT _____



5	48255-101-27	4.4 g
	HCl (4N)	5 ml
	CH$_2$Cl$_2$	10 ml

To a solution of 48255-101-27 in CH$_2$Cl$_2$ at -10°C, a solution of 4N HCl in dioxane was added dropwise (a lot of bubbles). The reaction was stirred at -10°C for 30 min. HCl was evaporated by a vacuum pump without heating. The rest of solution was warmed to RT. Evaporation was without heat to give a yellow oil. 4.4g

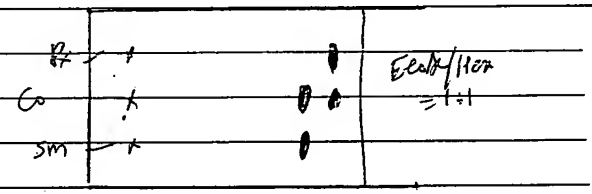
48255-102 HCl

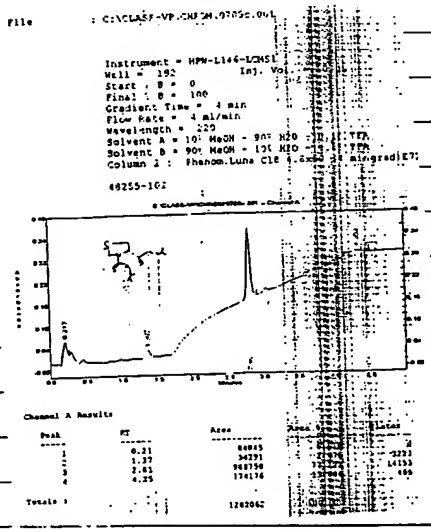
LC-MS M+H = 188

^{1}H NMR was consistent.

^{13}C NMR

RQ 22935. 7K2703 M-1 = 263.9





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CROSS REFERENCES:

ATTACHMENT E

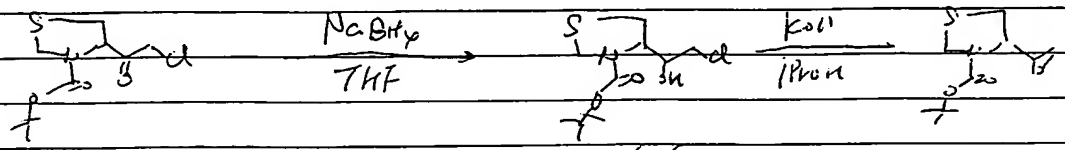
DO NOT WRITE IN THIS MARGIN

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE

No. 48255-103

DATE: ____ PROJ. NO. 08001 EXPT. NO. ____

SUBJECT ____



5	48255-102-1X	4.4 g	16.6 mmol
	NaBH4	614 mg	16.6 mmol
	THF	30 ml	

To a solution of 48255-102-1X in THF at RT was added $NaBH_4$. The reaction was stirred at RT for 30 min. LC-ms showed no SM left. HOAc was added to quench the reaction. EtOAc was added and the solution was washed with sat'd $NaHCO_3$, brine and dried over $MgSO_4$. Evaporation gave a crude oil. 48255-103-13

LC-ms showed right M+23 = 2% two isomer ratio 3:1

To a solution of 48255-103-13 in iPrOH (10 ml) was added 4N KOH (10 ml). The mixture was stirred at RT for 1h. EtOAc was added and the organic layer was washed with sat'd $NaHCO_3$, brine and dried over $MgSO_4$. Evaporation gave a crude oil. 48255-103-78

^{1}HNMR showed two isomer ratio = 2:1

Purification was performed by flash Chromatography on silica gel, loaded with crude, eluted with 8% EtOAc in hex. Pure fractions were combined and evaporated to give a colorless oil ~~48~~

Isomer I 48255-103-23 1.2 g

^{1}HNMR and ^{13}CNMR were consistent.

RQ 23050, TR 27387 MS: M+1 = 232.

Isome. II 48255-103-27 1.6 g

RQ 23054

TR 27390 M+1 = 232

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CROSS REFERENCES:

ATTACHMENT F

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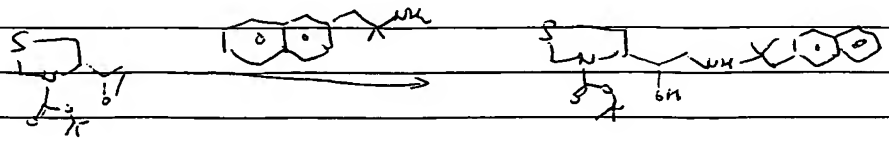
DATE _____ PROJ. NO. 08007 EXPT. NO. _____

SUBJECT _____



5	48255-103-23	500 mg	2.17 mmol
	Amine	432 mg	2.17 mmol

The mixture of 48255-103-23 and amine was heated together at 90°C for 3 hr. TLC and LC-MS showed no epoxide left. The reaction was cooled to RT. Purification was performed by flash chromatography on silica gel, loaded with CH2Cl2, eluted with 3% MeOH in CH2Cl2 + 0.2% NH4OH. Pure fractions were combined and evaporated to give a colorless oil.

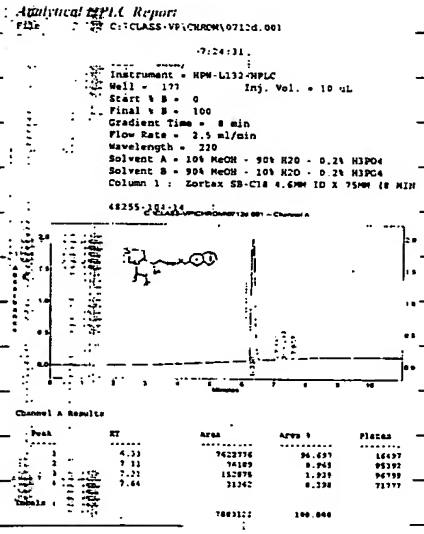
48255-106-1C 833 mg (87%)

KQ 23057 BMS-538174-01

MS (TR2735W) M+1 = 731

1HNMR

13CNMR were consistent.



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CROSS REFERENCES:

ATTACHMENT 6

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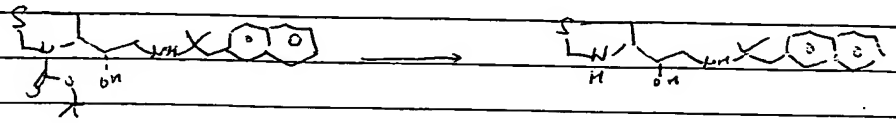
No. 48255-105

DATE: _____ PROJ. NO. 08007 EXPT. NO. _____

SUBJECT _____

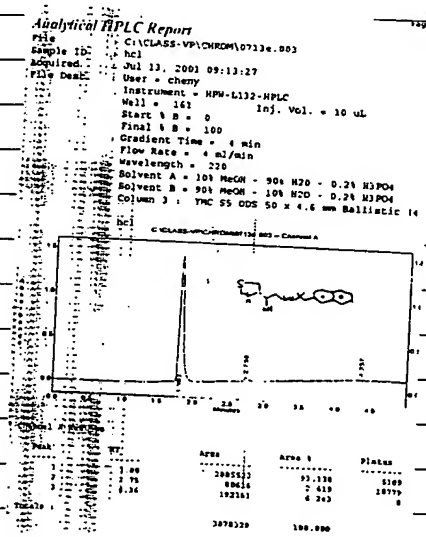


5	48255-104-1C	803 mg
	HCl in dioxane	20 ml
	THF	10 ml

To a solution of 48255-104-1C in THF at RT was added 4N HCl in dioxane. The reaction was stirred at RT for 24 hr. Then evaporated to dryness. The residue was dissolved in Sat'd $NaHCO_3$, EtOAc was added and the organic layer was washed with brine and dried over $MgSO_4$. Evaporation gave a pale-yellow oil.

48255-104-1C

^1H NMR
^{13}C NMR were consistent. RQ



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CROSS REFERENCES:

ATTACHMENT H

No. 48255-108

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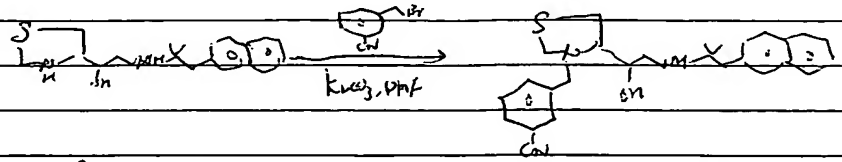
DATE: _____ PROJ. NO. 08667 EXPT. NO. _____

SUBJECT _____



5	48255-105-14	100 mg	0.3 mmol
	2-bromotoluenitrile	60 mg	0.3 mmol
	K_2CO_3	42 mg	0.3 mmol
	DMF	2 ml	

The mixture of 48255-105-14, 2-bromotoluenitrile and K_2CO_3 in DMF was stirred at 40°C for 5 hr, then cooled to RT, stirring was continued over weekend (3 days). EtOAc was added to the the reaction and the solution was washed with H_2O (two times), brine and dried over $MgSO_4$. Purification was performed by flash Chromatography on silica gel, loaded with CH_2Cl_2, eluted with 8% MeOH in CH_2Cl_2 with 0.2% NH_4OH. Pure fractions were combined and evaporated to give a white foam. HPLC showed small impurities. Purified again by flash column, loaded with CH_2Cl_2, eluted with 1% MeOH in EtOAc. Pure fractions were combined and evaporated to give a foam.

48255-108-20

48255-108-20 was dissolved in MeOH. HCl in EtOAc (1N / 1ml) was added. The mixture was stirred at RT for 30 min then evaporated to dryness. 120 mg

48255-108-20.

RQ23496

MS (Nominal)

MS (Accurate)

EA

OR

Pka

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CROSS REFERENCES:

ATTACHMENT I

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